https://doi.org/10.22416/1382-4376-2022-32-2-85-92

COVID-19 Pandemic and Irritable Bowel Syndrome — is there a Relationship?

Vadim A. Akhmedov

Omsk State Medical University, Omsk, Russia

The aim: to reflect the features of the course of irritable bowel syndrome during the COVID-19 pandemic.
Key points. It has been noted that the COVID-19 may contribute to the formation of post-infectious functional gastrointestinal diseases, given that angiotensin-converting enzyme-2 (ACE-2) receptors, the site of binding of the SARS-CoV-2 virus to human cells, are also present in epithelial intestinal cells; virus was found in feces in about half of patients, gastrointestinal symptoms, including diarrhea occur in about one fifth of patients, fecal calprotectin, a marker of GI inflammation is elevated in patients with COVID-19, macroscopically as well as histologically, patients show signs of damage mucous membrane of the gastrointestinal tract, and also, as noted above, they have a dysbiosis of the intestinal microbiota.
Conclusion. It was shown that during the pandemic, more than 90 % of the interviewed patients with IBS had an exacerbation of IBS with an increase in symptoms such as bloating and cramps, and 75 % of them said that the exacerbation of symptoms was reflected in the activity of patients in everyday life. These factors dictate the need for an integrated approach in the management of such a group of patients with the use of modern multi-target drugs that affect the pathogenetic factors in the formation of functional gastrointestinal diseases, one of which is the Kolofort drug due to the triple multi-target mechanism of action on the pathogenesis of functional gastrointestinal diseases.
Keywords: irritable bowel syndrome, COVID-19, microbiota, stress, dysbiosis, Kolofort
Conflict of interest: Publication was supported by “Materia Medica”.

For citation: Akhmedov V.A. COVID-19 Pandemic and Irritable Bowel Syndrome — is there a Relationship? Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2022;32(2):85–92. https://doi.org/10.22416/1382-4376-2022-32-2-85-92

Пандемия COVID-19 и синдром раздраженного кишечника — есть ли связь?

В.А. Ахмедов

ФГБОУ ВО «Омский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Омск, Российская Федерация

Цель обзора — отразить особенности течения синдрома раздраженного кишечника (СРК) в период пандемии COVID-19.
Основные положения. Отмечено, что COVID-19 может способствовать формированию постинфекционных функциональных желудочно-кишечных заболеваний из-за ряда предрасполагающих факторов. Рецепторы ангиотензинпревращающего фермента-2 (АПФ-2), место связывания вируса SARS-CoV-2 с клетками организма человека, присутствуют в эпителиальных клетках кишечника; вирус был обнаружен в кале примерно у половины пациентов. Желудочно-кишечные симптомы, в том числе диарея, возникают примерно у одной пятой пациентов. Фекальный кальпротектин, маркер воспаления ЖКТ, повышен у пациентов с COVID-19. У пациентов отмечены макроскопические и микроскопические признаки повреждения слизистой оболочки ЖКТ. COVID-19 ассоциирован с изменением кишечной микробиоты. В условиях пандемии COVID-19 у более чем 90 % из опрошенных пациентов с СРК выявлено обострение заболевания с усилением боли и вздутия живота.
Заключение. Ведение пациентов с СРК в условиях пандемии COVID-19 диктует необходимость комплексного подхода. Примером мультитаргетного препарата, оказывающего влияние на различные патогенетические факторы функциональных заболеваний ЖКТ, служит препарат Колофорт®.
Ключевые слова: синдром раздраженного кишечника, COVID-19, микробиота, стресс, дисбиоз, Колофорт®
Конфликт интересов: Публикация выполнена при поддержке «Материа Медика».

Для цитирования: Ахмедов В.А. Пандемия COVID-19 и синдром раздраженного кишечника — есть ли связь? Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2022;32(2):85–92. https://doi.org/10.22416/1382-4376-2022-32-2-85-92

Currently the world evidences a serious crisis in public healthcare system triggered by the new coronavirus infection COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first discovered at the end of 2019 [1]. In addition to pulmonary manifestations the virus is capable of causing gastrointestinal signs. The most common gastrointestinal COVID-19 symptoms include nausea, vomiting, diarrhea and abdominal pain [2]. Recently the clinical studies demonstrated increased incidence of gastrointestinal symptoms in COVID-19 patients, with diarrhea being the most common symptom with incidence varying between 2 % and 50. The differences vary depending on age, various co-morbidities, region, lifestyle and eating habits [3]. Meanwhile, long-term gastrointestinal sequelae of SARS CoV-2 have not been elucidated [4].

Correlation between impaired intestinal microbiota and irritable bowel syndrome (IBS) has been established [5]. Currently there have been discovered numerous factors associated with increased risk of postinfectious IBS (PI-IBS) such as feminine gender, young age, smoking, stool frequency and diarrhea > 1 week, abdominal pain, rectal bleeding, antibacterial therapy, anxiety, depression, somatization, neuroticism, recent unpleasant life events, hypochondria, extraversion, negative disease ideas, history of stress, sleep disorders and aggravated family history of functional gastrointestinal disorders [6]. COVID-19 pandemic is known to be associated with a lot of these risk factors for PI-IBS both psychosomatically and in terms of active antibiotic therapy, especially in hospital management. Chronic inflammation and modified intestinal permeability were detected in IBS patients with prevailing diarrhea (IBS-D) including PI-IBS [7].

Unsurprisingly, COVID-19 may result in development of post-infectious functional gastrointestinal disorders [8]. Angiotensin-converting enzyme-2 (ACE-2) receptors, the site of SARS-CoV-2 virus binding to human cells are also found in epithelial intestinal cells. The virus was detected in feces in approximately 50 % patients, gastrointestinal symptoms including diarrhea occur in one in five patients. Fecal calprotectin (marker of gastrointestinal (GI) inflammation) is elevated in patients with COVID-19. Macroscopic and histological signs of GI mucosa lesions were recorded. As mentioned above, changes in intestinal microbiota were found in such patients [9–11]. In COVID-19 patients increased intestinal mucosa permeability was also detected [12]. In a recent systematic review and meta-analysis intestinal permeability was more commonly increased in patients with PI-IBS (4/4 studies) and IBS-D (9/13 studies) comparted to those with IBS with prevailing constipations (IBS-3; 2/7 studies) [13]. Patients with I-IBS showed increased inflammatory cellular infiltration and higher levels of mRNA of pro-inflammatory cytokine interleukin-1β (IL-1β) in rectal biopsy specimens in reverse-transcriptase polymerase chain reaction assay even 3 months after resolution of the signs of acute gastroenteritis [14]. Patients with PI-IBS were also found to have increased levels of IL-6, pleiotropic cytokine activating the inflammatory nuclear factor transcription pathway (NF)-kB compared to healthy control subjects [15].

Certainly, individual genetic factors are essential in defining long-term inflammatory response after an intestinal infection. In particular, some patients had polymorphisms in several genes of pro- and anti-inflammatory cytokines which may play an important role in further body response after acute gastroenteritis. Investigation of gene polymorphism revealed tendency for association of mononucleotide polymorphisms of the genes involved in immune and intestinal epithelial barrier pathways and localized in TLR9 (coding pattern recognition receptor [rs352139 and P545P]), CDH1 (coding dense connective tissue [rs16260, -C160A]) and IL-6 (rs1800795, -G174C) associated with development of PI-IBS [16]. Another study detected polymorphism of TNFα which was associated with development of PI-IBS after a *Campylobacter jejuni* infection [17]. Patients with IBS-D and PI-IBS also had higher serotonin levels in rectal mucosa and polymorphism of serotonin reuptake gene compared to control group [18].

Intestinal microbiota in IBS patients is less diverse compared to healthy subjects. Similar phenomenon is observed in patients with PI-IBS

being relatively more abundant in *Bacteroidetes* (including *Bacteroides* and *Prevotella*) and having relatively lower count of *Firmicutes* such as *Clostridia* compared to control group [17]. Detailed analysis of additional data is clearly needed to evaluate whether such changes in intestinal microbiota are the cause or the consequence of acute gastroenteritis with development of PI-IBS or changes in diet, antibacterial therapy and impaired intestinal motility could be responsible [18]. However, as intestinal microbiota affects intestinal motility, visceral hypersensitivity, immune response, mental dysfunction, sleep, impaired serotonin and bile acid metabolism, the role of intestinal dysbiosis in PI-IBS pathogenesis should not be underestimated [17].

One of the explanations for increased incidence of diarrhea in post-COVID-19 patients also lies in modified microbial composition of intestinal microbiota. Presence of SARS-CoV-2 in gastrointestinal tract does not always cause gastrointestinal symptoms. In a Singapore study 50 % examined patients with COVID-19 had detectable levels of fecal virus, however only half of them experienced gastrointestinal symptoms such as diarrhea [20]. A recent study demonstrated significantly reduced diversity in intestinal microbiota specimens collected from COVID-19 patients compared to those from healthy subjects [21]. The same study reported enriched opportunistic microbiota in COVID-19 patients as well as depletion of good bacteria including *Ruminococcaceae* and *Lachnospiraceae*.

Patients with COVID-19 treated with antibiotics upon admission showed further depletion of bacteria, especially symbionts playing positive role for host immunity including *Faecalibacterium prausnitzii*, *Lachnospiraceae 5_1_63 FAA*, *Eubacterium rectale, Ruminococcus obeum* and *Dorea formicigenerans* bacteria [22]. Changes in intestinal microbial composition persisted throughout COVID-19 infection and even within several months after respiratory SARS-CoV-2 clearance [23]. Similar results were demonstrated in other studies showing similar pattern of impaired intestinal microbiota in COVID-19 patients [24]. Meanwhile, the bacteria producing butyrate such as *Faecalibacterium prausnitzii, Clostridium butyricum, Clostridium leptum* and *Eubacterium rectale* were significantly less represented in COVID-19 patients compared to control [25]. In feces of COVID-19 patients relative predominance of common opportunistic *Enterobacteriaceae* and enterococci as well as increased prevalence of opportunistic *Streptococcus, Rothia, Veillonella* and *Actinomyces* was also detected compared to control group, while *Romboutsia, Faecalibacterium* and *Fusicatenibacter* were predominant in the feces of healthy control subjects [22].

Six-month follow-up of intestinal microbiota in COVID-19 patients revealed significantly reduced species richness (CHAO1 index) in intestinal microbiome at all disease stages — during exacerbation, recovery and post COVID-19 recovery [26] In addition, COVID-19 patients had markedly reduced intestinal bacterial diversity. Microbial diversity is known to be an essential factor defining stability of microbial ecosystem [27]. Stable ecosystems provide colonizational resistance to opportunistic organisms. Therefore, reduced diversity and richness of intestinal microbiota may be associated with excessive growth of opportunistic bacteria and exhibit negative long-term impact on COVID-19 patients which may be an additional stimulus for PI-IBS development [28].

Patients with marked intestinal SARS-CoV-2 contamination were abundant with *Collinsella aerofaciens, Collinsella tanakaei, Streptococcus infantis* and *Morganella morganii* and also showed high functional capacity for biosynthesis of nucleotides de novo, biosynthesis of amino acids and glycolysis [29]. Furthermore, hyperinflammatory reaction in patients was associated with impaired intestinal permeability and microbial translocation [30]. Levels of fecal calprotectin, a marker of intestinal inflammation, were increased in COVID-19 patients secondary to translocation of granulocytes and monocytes/macrophages to intestinal lumen additionally suggesting immune intestinal impairment and modified intestinal microbiome in COVID-19 patients [31]. Oppositely, in those with low SARS-CoV-2 intestinal contamination or lack of infection high levels of bacteria producing short-chain fatty acids (SCFA) (*Alistipes onderdonkii, Parabacteroides merdae, Bacteroides stercoris* and *Lachnospiraceae 1_1_57 FAA*) was reported [29].

Based on the survey, respondents with IBS experienced general aggravation of emotional, social and mental well-being compared to those without IBS [32]. The survey also demonstrated that those with IBS were less compliant with social distancing rules compared to those without IBS. In addi-

tion, the patients with aggravated IBS symptoms during the pandemic were also less inclined to follow personal hygiene recommendations and wished social distancing restrictions were cancelled as soon as possible. Stronger emotional problems correlated with IBS severity. Among the respondents without history of IBS, 4.7 % developed IBS-like symptoms within the first 3 months of COVID-19 pandemic. Quite unexpected was a higher percentage of respondents with IBS with either stable or even improved condition during the pandemic despite the predicted aggravation of IBS symptoms. This phenomenon was called The Paradox of Covid-19 Pandemic by the investigators.

Functional gastrointestinal disorders are known to directly correlate with occupational stress or emotional burn-out [33]. Forced experiment of remote work in 2020 may also give an insight on such work experience among those with IBS. The outcomes of the pandemic confirmed the previous data that flexible work commonly suggests a longer work-day while also providing other benefits such as reduced emotional burn-out, satisfaction with work and improved overall well-being. These factors are essential for patients with functional GI disorders [34].

For IBS patients dependent on environmental factors the stress related to work trips is important also supporting the benefit of flexible working time for this cohort. Hypothesis on flexible work and work trips to and from using public transport as the factors affecting IBS severity was confirmed in a recent Japanese study which detected that these are improvement factors for the patients with functional dyspepsia and IBS [35].

A certain role in IBS course in pandemic settings belongs to modified eating habits, food availability when IBS patients stayed at home to observe social distancing which could be associated with reduced physical activity and overeating. In a survey in Italy 46.1 % respondents reported overeating during social withdrawal, 19.5 % gained weight, increased consumption of "comfort" foods, in particularly chocolate, ice-cream, desserts (42.5 %) and salty snacks (23.5 %) [36]. Modified diet quality may also affect mental health and well-being impacting the symptoms of IBS patients [37].

Therefore, it is extremely important to assure local availability of diverse foods for IBS patients by means of adequate logistics and timely transportation of food products [38]. The diet with low levels of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) may improve the listed IBS symptoms, while some authors consider impaired delivery of fermentable oligosaccharides, disaccharides, monosaccharides and polyol-containing products with food as unfriendly for the intestines [39]. WHO survey in 155 countries in May 2020 revealed that medical servicing was partially or fully failed in a lot of countries, while 53 % countries reported full or partial lack of control over hypertension, 49 % — diabetes mellitus and its sequelae. An interruption in follow-up and pharmacotherapy of IBS patients could have affected the disease course [40]. A Saudi Arabian study demonstrated that more than 90 % surveyed patients with IBS experienced an IBS exacerbation during the pandemic with reinforced symptoms such as bloating and cramps; 75 % of them claimed their exacerbation affected their daily life. Meanwhile, 18 % respondents admitted they started sedative therapy to minimize stress [41]. Despite strong impact of COVID-19-related stress on IBS symptoms, only 20 % study subjects consulted their physicians which could be due to fear of getting contaminated from other clinic visitors as well as due to difficult arrangement of a medical visit resulting from limited mobility and number of scheduled consultations.

Diet adjustment is deemed to be a convenient and safe way to reduce the risk of SARS-CoV-2 morbidity and if contaminated — to relieve its severity. Food fibers modify the composition of intestinal microflora and increase relative proportion of SCFAs showing anti-inflammatory properties via fatty acid receptors such as рецептор, связанный с G-белком (GPCR) 41 и 43 [42]. As the dietary limitation in fermentable oligo-, di-, monosaccharides and polyols were positive in relieving IBS symptoms, such limitation is expected to be beneficial for PI-IBS as well [43]. Also, studies of FODMAP diet on PI-IBS patients are currently lacking.

Visceral neuromodulators, especially tricyclic antidepressants, may be of benefit in the treatment of PI-IBS as they generally relieve diarrhea manifestations due to their anticholinergic effect [44]. However, dedicated clinical studies have not been performed either.

Recently of great interest is the treatment of COVID-19 patients by regulating intestinal microbiota. This is especially relevant for the patients

with pre-existing IBS or post-infection PI-IBS. An open-label pilot study (NCT04950803) demonstrated that 4-week oral probiotic formula (S1M01) accelerated recovery, increased immunity and reduced serum concentration of pro-inflammatory cytokines in hospitalized COVID-19 patients. Fecal enrichment with good bacteria using this probiotic formula was observed 5 weeks post therapy compared to control group not treated with probiotics [45]. According to another study, all patients with COVID-19 receiving probiotic formula Sivomixx® had diarrhea and other symptoms resolved such as bloating, gurgling, tenesmi within 72 hours compared to < 50 % patients in control group [46].

The positive role of probiotics in IBS patients was reflected in clinical recommendations by Russian Gastroenterological Association 2021 specifying that IBS patients should be treated with antidiarrheal biological products regulating intestinal microflora or dietary supplements (DS), i.e. probiotics to relieve abdominal pain, normalize stool frequency and consistency which may also be relevant for patients with post-COVID PI-IBS [47].

Given numerous pathogenetic COVID-19 factors affecting IBS, the treatment should be multitargeted; meanwhile minimum daily doses should be suggested to increase treatment compliance. Research and Manufacturing Company OOO "NPF "Materia Medical Holding" (Moscow, Russia) has developed and implemented a multi-target combination product Kolofort, a combination of released active forms (RA) of antibodies (Ab) to S-100 protein, TNF-α and histamine (H) for the treatment of functional GI disorders. Therefore, the product has anti-inflammatory, spasmolytic and anxiolytic effects and affects the mechanisms of IBS pathogenesis [48] including under COVID-19 settings.

Observational program "COMFORT" carried out in Russia enrolled 14 362 patients. The program was designed to evaluate efficacy and safety of combination of RA Ab to S-100, Ab to TNF-α and Ab to H in patients with functional dyspepsia (FD), IBS and their combination [49]. The study results demonstrate that combination of RA Ab to S-100, Ab to TNF-α and Ab to H exhibits marked therapeutic effect, reducing intensity of the symptoms of functional GI disorders by ≥ 50 % in 80 % patients. Therapy with combination of RA Ab to S-100, Ab to TNF-α and Ab to H was associated with a more pronounced increase un the number of patients considered as "healthy" and "borderline disorder". Proportion of patients considered as "healthy" was 22.33 % (537) in FD group; 20.93 % (1237) in IBS group and 16.57 % (156) in FD + IBS group. The cohort of patients with borderline disorder included 1339 (55.69 %) patients with FD, 3044 (51.51 %) with IBS and 488 (51.85 %) patients with their combination. Observational program "COMFORT" demonstrated positive effect of combination of RA Ab to S-100, Ab to TNF-α and Ab to H in most patients with FD + IBS: in 83 % cases total "7 per 7" questionnaire score decreased by ≥ 50 %. Therefore, based on "COMFORT" results, combination of RA Ab to S-100, Ab to TNF-α and Ab to H was effective in the treatment of patients with FD, IBS and FD + IBS [49]. In the absence of clear recommendations on pharmacotherapy of combination of functional disorders, the evidence of effective therapy of this population is an important result of this study. Combination of RA Ab to S-100, Ab to TNF-α and Ab to H was tolerated well, did not have negative impact on patients' health which is relevant for long-term therapy of functional disorders. "COMFORT" results suggest that Kolofort administration to patients with post-COVID-19 functional disorders may be pathogenetically justified based on multi-factor effect of the new coronavirus infection on development of gastrointestinal functional disorders.

Therefore, the key features of IBS during new coronavirus infection pandemic include increased incidence of PI-IBS and aggravation of stress factor associated with fear of getting contaminated, inability to make a scheduled medical visit. Meanwhile, there is a number of positive aspects including minimization of stress due to remote working and other activities. There is a clear need in an integrated approach to managing such population using modern multi-target products addressed at pathogenetic factors of functional GI disorders which are aggravated directly by the virus impact on the body and by the consequences of treatment of the new coronavirus infection. Based on the results of observational program "COMFORT" Kolofort may be considered as such product due to its multi-target mechanism of action on pathogenesis of functional GI disorders.

Reference / Литература

1. *Munster V.J., Feldmann F., Williamson B.N., van Doremalen N., Perez-Perez L., Schulz J., et al.* Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. 2020;585(7824):268–72. DOI: 10.1038/s41586-020-2324-7
2. *Hamid S., Mir M. Y., Rohela G.K.* Novel coronavirus disease (COVID-19): a pandemic (epidemiology, pathogenesis and potential therapeutics). New Microbes New Infect. 2020;35:100679. DOI: 10.1016/j.nmni.2020.100679
3. *D'Amico F., Baumgart D.C., Danese S., Peyrin-Biroulet L.* Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. Clin Gastroenterol Hepatol. 2020;18(8):1663–72. DOI: 10.1016/j.cgh.2020.04.001
4. *Ianiro G., Mullish B.H., Kelly C.R., Sokol H., Kassam Z., Ng S.C., et al.* Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel. Lancet Gastroenterol Hepatol. 2020;5(5):430–2. DOI: 10.1016/S2468-1253(20)30082-0
5. *Takakura W., Pimentel M.* Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome – An Update. Front Psychiatry. 2020;11:664. DOI: 10.3389/fpsyt.2020.00664
6. *Klem F., Wadhwa A., Prokop L.J., Sundt W.J. Farrugia G., Camilleri M., et al.* Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. Gastroenterology 2017;152:1042–54. DOI: 10.1053/j.gastro.2016.12.039
7. *Ghoshal U.C., Ranjan P.* Post-infectious irritable bowel syndrome: the past, the present and the future. J Gastroenterol Hepatol. 2011;26 (Suppl 3):94–101. DOI: 10.1111/j.1440-1746.2011.06643.x
8. *Schmulson M., Ghoshal U.C., Barbara G.* Managing the inevitable surge of post-COVID-19 functional gastrointestinal disorders. Am J Gastroenterol. 2021;116:4–7. DOI: 10.14309/ajg.0000000000001062
9. *Ghoshal U.C., Ghoshal U., Mathur A., Singh R.K., Nath A.K., Garg A., et al.* The spectrum of gastrointestinal symptoms in patients with coronavirus disease-19: predictors, relationship with disease severity, and outcome. Clin Transl Gastroenterol. 2020;11:e00259. DOI: 10.14309/ctg.0000000000000259
10. *Wan Y., Shang J., Graham R., Baric R.S., Li F.* Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94:e00127-20. DOI: 10.1128/JVI.00127-20
11. *Wong M.C., Huang J., Lai C., Ng R., Chan F.K., Chan P.K.* Detection of SARS-CoV-2 RNA in fecal specimens of patients with confirmed COVID-19: a meta-analysis. J Infect 2020;81:e31–8. DOI: 10.1128/JVI.00127-20
12. *Cardinale V., Capurso G., Ianiro G., Gasbarrini A., Arcidiacono P.G., Alvaro D.* Intestinal permeability changes with bacterial translocation as key events modulating systemic host immune response to SARS-CoV-2: a working hypothesis. Dig Liver Dis. 2020;52:1383–9. DOI: 10.1016/j.dld.2020.09.009
13. *Hanning N., Edwinson A.L., Ceuleers H., Peters S.A., De Man J.G., Hassett L.C., et al.* Intestinal barrier dysfunction in irritable bowel syndrome: a systematic review. Therap Adv Gastroenterol. 2021;14:1756284821993586. DOI: 10.1177/1756284821993586
14. *Gwee K.A., Collins S.M., Read N.W., Rajnakova A., Deng Y., Graham J.C., et al.* Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome. Gut. 2003;52(4):523–6. DOI: 10.1136/gut.52.4.523
15. *Downs I.A., Aroniadis O.C., Kelly L., Brandt L.J.* Postinfection irritable bowel syndrome: the links between gastroenteritis, inflammation, the microbiome, and functional disease. J Clin Gastroenterol. 2017;51:869–77. DOI: 10.1097/MCG.0000000000000924
16. *Villani A.C., Lemire M., Thabane M., Belisle A., Geneau G. , Garg A.X., et al.* Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. Gastroenterology. 2010;138:1502–13. DOI: 10.1053/j.gastro.2009.12.049
17. *Tang H.Y., Jiang A.J., Wang X.Y., Wang H., Guan Y.Y., Li F., et al.* Uncovering the pathophysiology of irritable bowel syndrome by exploring the gut-brain axis: a narrative review. Ann Transl Med. 2021;9(14):1187. DOI: 10.21037/atm-21-2779
18. *Barbara G., Grover M., Bercik P., Corsetti M., Ghoshal U.C., Ohman L., et al.* Rome Foundation Working Team report on post-infection irritable bowel syndrome. Gastroenterology 2019;156(1):46–58. DOI: 10.1053/j.gastro.2018.07.011
19. *Ghoshal U.C., Shukla R., Ghoshal U., Gwee K.A., Ng S.C., Quigley E.M.* The gut microbiota and irritable bowel syndrome: friend or foe? Int J Inflam 2012;2012:151085. DOI: 10.1155/2012/151085
20. *Ong J., Young B.E., Ong S.* COVID-19 in gastroenterology: a clinical perspective. Gut. 2020;69:1144–5. DOI: 10.1136/gutjnl-2020-321051
21. *Gu S., Chen Y., Wu Z., Chen Y., Gao H., Lv L., et al.* Alterations of the gut microbiota in patients with COVID-19 or H1N1 influenza. Clin Infect Dis. 2020;71(10):2669–78. DOI: 10.1093/cid/ciaa709
22. *Rodrigues P.B., Dos Santos Pereira Gomes A.B., Genaro L.M., Pascoal L.B., de Souza A.P., Leal R.F.* Intestinal Microbiota in the SARS-CoV-2 Infection: What Is Known? Adv Exp Med Biol. 2021;1327:93–106. DOI: 10.1007/978-3-030-71697-4_7
23. *Tian Y., Sun K.Y., Meng T.Q., Guo S.M., Li G.M., Xiong G.L., et al.* Gut Microbiota May Not Be Fully Restored in Recovered COVID-19 Patients After 3-Month Recovery. Front Nutr. 2021;8:638825. DOI: 10.3389/fnut.2021.638825
24. *Gaibani P., D'Amico F., Bartoletti M., Lombardo D., Rampelli S., Fornaro G., et al.* The Gut Microbiota of Critically Ill Patients With COVID-19. Front Cell Infect Microbiol. 2021;11:670424. DOI: 10.3389/fcimb.2021.670424
25. *Sokol H., Contreras V., Maisonnasse P., Desmons A., Delache B., Sectio V., et al.* SARS-CoV-2 infection in nonhuman primates alters the composition and functional activity of the gut microbiota. Gut Microbes. 2021;13(1):1–19. DOI: 10.1080/19490976.2021.1893113
26. *Chen J., Hall S., Vitetta L.* Altered gut microbial metabolites could mediate the effects of risk factors in Covid-19. Rev Med Virol. 2021;31(5):1–13. DOI: 10.1002/rmv.2211
27. *Zhou Y., Zhang J., Zhang D. Ma V.L., Wang X., et al.* Linking the gut microbiota to persistent symptoms

in survivors of COVID-19 after discharge. Microbiol. 2021;59(10):941–8. DOI: 10.1007/s12275-021-1206-5
28. *Yamamoto S., Saito M., Tamura A., Prawisuda D, Mizutani T, Yotsuyanagi H.* The human microbiome and COVID-19: A systematic review. PLoS One. 2021;16(6):e0253293. DOI: 10.1371/journal.pone.0253293
29. *Zuo T., Zhang F., Lui G.C., Yeoh Y.K., Li A.Y.L., Zhan H., et al.* Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 2020;159:944–55.e8. DOI: 10.1053/j.gastro.2020.05.048
30. *Cardinale V., Capurso G., Ianiro G., Gasbarrin A., Arcidiacono P.G., Alvaro D.* Intestinal permeability changes with bacterial translocation as key events modulating systemic host immune response to SARS-CoV-2: A working hypothesis. Dig Liver Dis. 2020;52(12):1383–9. DOI: 10.1016/j.dld.2020.09.009
31. *Effenberger M., Grabherr F., Mayr L., Schwaerzler J., Nairz M., Seifert M., et al.* Faecal calprotectin indicates intestinal inflammation in COVID-19. Gut. 2020;69:1543–4. DOI: 10.1136/gutjnl-2020-321388
32. *Quek S.X.Z., Loo E.X.L, Demutska A, Chua C.E., Kew G.S., Wong S., et al.* Impact of the coronavirus disease 2019 pandemic on irritable bowel syndrome. J Gastroenterol Hepatol. 2021;36(8):2187–97. DOI: 10.1111/jgh.15466
33. *Nam Y., Kwon S.C., Lee Y.J., Jang E.C., Ahn S.H.* Relationship between job stress and functional dyspepsia in display manufacturing sector workers: a cross-sectional study. Ann Occup Environ. Med. 2018;30:62. DOI: 10.1186/s40557-018- 0274-4
34. *Felstead A., Henseke G.* Assessing the growth of remote working and its consequences for effort, well-being and work-life balance. New Technol Work Employ. 2017;32(3):195–212. DOI: 10.1111/ntwe.12097
35. *Oshima T., Siah K.T.H., Yoshimoto T., Miura K., Tomita T., Fukui H., et al.* Impacts of the COVID-19 pandemic on functional dyspepsia and irritable bowel syndrome: A population-based survey. J Gastroenterol Hepatol. 2021;36(7):1820–7. DOI: 10.1111/jgh.15346
36. *Scarmozzino F., Visioli F.* Covid-19 and the subsequent lockdown modified dietary habits of almost half the population in an Italian sample. Foods 2020;9(5):675. DOI: 10.3390/foods9050675
37. *Hislop T.G., Bajdik C.D., Balneaves L.G., et al.* Physical and emotional health effects and social consequences after participation in a low-fat, high-carbohydrate dietary trial for more than 5 years. J Clin Oncol. 2006;24(15):2311–7. DOI: 10.1200/JCO.2005.04.3042
38. *Liese A.D., Weis K.E., Pluto D., Smith E., Lawson A.* Food store types, availability, and cost of foods in a rural environment. J Am Diet Assoc. 2007;107(11):1916–23. DOI: 10.1016/j.jada.2007.08.012
39. *Barrett J.S.* Extending our knowledge of fermentable, short-chain carbohydrates for managing gastrointestinal symptoms. Nutr Clin Pract. 2013;28(3):300–6. DOI: 10.1177/0884533613485790
40. *Coroiu A., Moran C., Campbell T., Geller A.C.* Barriers and facilitators of adherence to social distancing recommendations during COVID-19 among a large international sample of adults. PLoS One. 2020;15:e0239795. DOI: 10.1371/journal. pone.0239795
41. *Alzahrani M.A., Alshamrani A.S., Ahmasani I.M., Alahmari F.S., Asiri A.H., Alshehri A.M.* Coronavirus disease 2019 pandemic stress and its effects on irritable bowel syndrome patients in Saudi Arabia. Medicine (Baltimore). 2020;99(51):e23711. DOI: 0.1097/MD.0000000000023711
42. *Conte L., Toraldo D.M.* Targeting the gut-lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection. Ther Adv Respir Dis. 2020;14:1753466620937170. DOI: 10.1177/1753466620937170
43. *Mehtab W., Agarwal A., Singh N., Malhotra A., Makharia G.K.* All that a physician should know about FODMAPs. Indian J Gastroenterol 2019;38:378–90. DOI: 10.1007/s12664-019-01002-0
44. *Ghoshal U.C.* Pros and cons while looking through an Asian window on the Rome IV criteria for irritable bowel syndrome: pros. J Neurogastroenterol Motil. 2017;23:334–40. DOI: 10.5056/jnm17020
45. *Zhang Q., Yue S., Wang W., Chen Y., Zhao C., Song Y., et al.* Potential Role of Gut Microbiota in Traditional Chinese Medicine against COVID-19. Am J Chin Med. 2021;49(4):785–803. DOI: 10.1142/S0192415X21500373
46. *d'Ettorre G., Ceccarelli G., Marazzato M., Campagna G., Pinacchio C., Alessandri F., et al.* Challenges in the management of SARS-CoV2 Infection: The role of oral bacteriotherapy as complementary therapeutic strategy to avoid the progression of COVID-19. Front. Med. 2020;7:389. DOI: 10.3389/fmed.2020.00389
47. *Ивашкин В.Т., Маев И.В., Шелыгин Ю.А., Баранская Е.К., Белоус С.С., Белоусова Е.А. и др.* Диагностика и лечение синдрома раздраженного кишечника (Клинические рекомендации Российской гастроэнтерологической ассоциации и Ассоциации колопроктологов России). Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2021;31(5):74–95. [*Ivashkin V.T., Maev I.V., Shelygin Yu.A., Baranskaya E.K., Belous S.S., Belousova E.A., et al.* Diagnosis and Treatment of Irritable Bowel Syndrome: Clinical Recommendations of the Russian Gastroenterological Association and Association of Coloproctologists of Russia. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2021;31(5):74–95 (In Russ.)]. DOI: 10.22416/1382-4376-2021-31-5-74-95
48. *Эртузун И.А., Зуева Е.П., Клылова С.Г., Ефимова Л.А., Дугина Ю.Л., Эпштейн О.И.* Экспериментальное изучение «Колофорта» – нового препарата для лечения синдрома раздраженного кишечника и других функциональных заболеваний желудочно-кишечного тракта. Вестник Волгоградского государственного медицинского университета. 2012;4(44):25–27. [Ertuzun I.A., Zueva E.P., Klylova S.G., Efimova L.A., Dugina Yu.L., Epstein O.I. Experimental study of preparation Kolofort – a novel drug for treatment of irritable bowel syndrome and other functional gastrointestinal disorders. Vestnik VolgGMU. 2012;4(44):25–27 (In Russ.)].
49. *Ivashkin V.T., Poluektova E.A., Glazunov A.B., Putilovskiy M.A., Epstein O.I.* Pathogenetic approach to the treatment of functional disorders of the gastrointestinal tract and their intersection: results of the Russian observation retrospective program COMFORT. BMC Gastroenterol. 2019;20(1):2. DOI: 10.1186/s12876-019-1143-5

Information about the author

Vadim A. Akhmedov — Dr. Sci. (Med.), Prof., Head of the Chair of Medical Rehabilitation of Additional Professional Education, Omsk State Medical University.
Contact information: v_akhmedov@mail.ru;
644099, Omsk, Lenina str., 12.
ORCID: https://orcid.org/0000-0002-7603-8481

Сведения об авторе

Ахмедов Вадим Адильевич — доктор медицинских наук, профессор, заведующий кафедрой медицинской реабилитации дополнительного профессионального образования ФГБОУ ВО «Омский государственный медицинский университет».
Контактная информация: v_akhmedov@mail.ru;
644099, г. Омск , ул. Ленина 12.
ORCID: https://orcid.org/0000-0002-7603-8481

Submitted: 25.01.2022 Accepted: 07.03.2022 Published: 15.05.2022
Поступила: 25.01.2022 Принята: 07.03.2022 Опубликована: 15.05.2022